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(54) VOIE DE SYNTHÈSE BIOLOGIQUE DES GENES DES 1-  
DESOXY-D-XYLULOSE

(54) GENES OF THE 1-DESOXY-D-XYLULOSE BIOSYNTHETIC  
PATHWAY

(57) The invention relates to the 1-desoxy- D-xylulose- 5-phosphate reductoisomerase gene, the 1-desoxy- D-xylulose- 5-phosphate- synthase gene and the gcpE gene of the 1-desoxy- D-xylulose biosynthetic pathway and to their use for transforming vectors, host organisms and plants and for determining substances that inhibit this biosynthetic pathway.



**PCT**  
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<p>(21) Internationales Aktenzeichen: <b>PCT/EP99/07055</b></p> <p>(22) Internationales Anmeldedatum: <b>22. September 1999 (22.09.99)</b></p> <p>(30) Prioritätsdaten:</p> <table style="width: 100%;"> <tr> <td style="width: 30%;">198 43 279.8</td> <td style="width: 30%;">22. September 1998 (22.09.98)</td> <td style="width: 40%;">DE</td> </tr> <tr> <td>199 23 567.8</td> <td>21. Mai 1999 (21.05.99)</td> <td>DE</td> </tr> </table> <p>(71)(72) Anmelder und Erfinder: <b>JOMAA, Hassan [DE/DE];</b> <b>Breslauer Strasse 24, D-35398 Gießen (DE).</b></p> <p>(74) Anwälte: <b>PANTEN, Kirsten usw.; Reichel und Reichel, Park-</b> <b>strasse 13, D-60322 Frankfurt am Main (DE).</b></p>		198 43 279.8	22. September 1998 (22.09.98)	DE	199 23 567.8	21. Mai 1999 (21.05.99)	DE	<p>(81) Bestimmungsstaaten: <b>AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</b></p> <p><b>Veröffentlicht</b> <i>Ohne internationalen Recherchenbericht und erneut zu veröffentlichen nach Erhalt des Berichts.</i></p>
198 43 279.8	22. September 1998 (22.09.98)	DE						
199 23 567.8	21. Mai 1999 (21.05.99)	DE						
<p>(54) Title: <b>GENES OF THE 1-DESOXY-D-XYLULOSE BIOSYNTHETIC PATHWAY</b></p> <p>(54) Bezeichnung: <b>GENE DES 1-DESOXY-D-XYLULOSE-BIOSYNTHESEWEGS</b></p> <p>(57) Abstract</p> <p>The invention relates to the 1-desoxy- D-xylulose- 5-phosphate reductoisomerase gene, the 1-desoxy- D-xylulose- 5-phosphate-synthase gene and the gcpE gene of the 1-desoxy- D-xylulose biosynthetic pathway and to their use for transforming vectors, host organisms and plants and for determining substances that inhibit this biosynthetic pathway.</p> <p>(57) Zusammenfassung</p> <p>Die vorliegende Erfindung betrifft das 1-Desoxy- D-xylulose- 5-phosphatreduktisomerase -Gen, das 1-Desoxy- D-xylulose- 5-phosphat- Synthase- Gen und das gcpE-Gen des 1-Desoxy- D-xylulose- Biosynthesewegs und ihre Verwendung zur Transformation von Vektoren, Wirtsorganismen und Pflanzen und zur Bestimmung von Stoffen, die diesen Biosyntheseweg inhibieren.</p>								

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Claims

1. DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 2 or for an analogue or derivative of the polypeptide according to SEQ ID no. 2, in which one or more amino acids have been deleted, added or replaced by other amino acids, wherein the enzymatic action of the polypeptide is retained, and which sequences originate from parasites, wherein sequence variations occurring within the framework of natural strain variability are included.
2. DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 4 or for an analogue or derivative of the polypeptide according to SEQ ID no. 4, in which one or more amino acids have been deleted, added or replaced by other amino acids, wherein the enzymatic action of the polypeptide is retained, and which sequences originate from parasites, wherein sequence variations occurring within the framework of natural strain variability are included.
3. DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 6 or for an analogue or derivative of the polypeptide according to SEQ ID no. 6, in which one or more amino acids have been deleted, added or replaced by other amino acids wherein the catalytic function of the polypeptide is retained.

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4. DNA sequence according to one of claims 1 to 3, characterised in that it also comprises functional regulation signals, in particular promoters, operators, enhancers, ribosomal binding sites.
5. DNA sequence with the following sub-sequences
- i) promoter which is active in viruses, eukaryotes and prokaryotes and ensures the formation of an RNA in the intended target tissue or target cells,
  - ii) DNA sequences according to one of claims 1 to 3,
  - iii) 3' untranslated sequence which, in viruses, eukaryotes and prokaryotes, results in the addition of poly(A) residues onto the 3' end of the RNA.
6. Process for the production of transgenic viruses, eukaryotes and prokaryotes for modifying the isoprenoid content, characterised in that a DNA sequence according to claim 4 or 5 is transferred and incorporated into the genome of viruses, eukaryotic and prokaryotic cells with or without use of a vector.
7. Transgenic systems, in particular plants and plant cells which contain one or more DNA sequences according to claims 1 to 5 as "foreign" or "additional" DNA, which sequences are expressed.
8. Expression vector containing one or more DNA sequences according to claims 1 to 5.

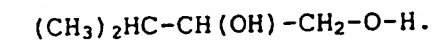
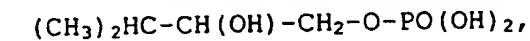
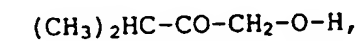
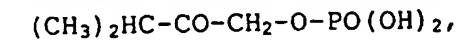
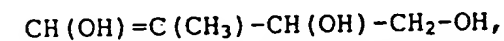
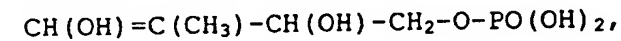
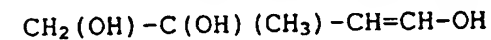
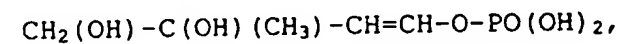
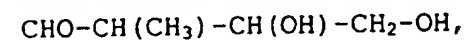
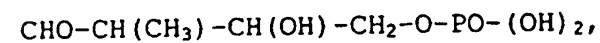
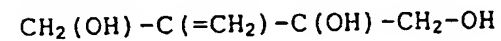
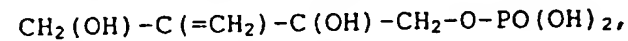
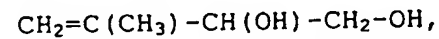
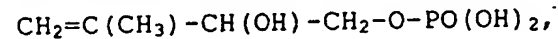
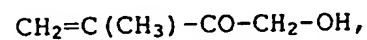
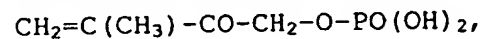
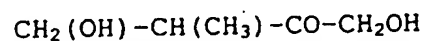
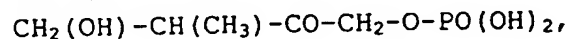
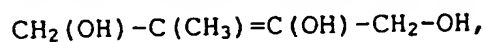
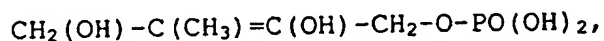
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9. Protein which is involved in the 1-deoxy-D-xylulose 5-phosphate metabolic pathway and a) is coded by DNA sequences SEQ ID no. 1, 3 or 5 or b) is coded by DNA sequences which hybridise with DNA sequences SEQ ID  
5 no. 1, 3, 5 or fragments of these DNA sequences in the DNA region which codes for the mature protein.
10. Protein according to claim 9, obtainable from the culture supernatants of parasites or from the  
10 disrupted parasites and purification by chromatographic and electrophoretic methods.
11. Protein according to one of claims 9 and 10, characterised in that it a) is the product of viral,  
15 prokaryotic or eukaryotic expression of exogenous DNA, b) is coded by sequences SEQ ID no. 1, 3 or 5 or is coded by DNA sequences which hybridise with DNA sequences SEQ ID no. 1, 3, 5 or fragments of these DNA sequences in the DNA region which codes  
20 for the mature protein, or c) is coded by DNA sequences which would hybridise without degeneration of the genetic code with the sequences defined in b) and which code for a polypeptide with a corresponding amino acid sequence.
- 25 12. Protein according to one of the preceding claims, characterised in that it comprises the amino acid sequences SEQ ID no. 2, 4 or 6.
- 30 13. Process for determining the enzymatic activity of the gcpE protein, characterised in that phosphorylation of a sugar or of a phosphorus sugar or of a precursor of isoprenoid biosynthesis, in

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particular the phosphorylation of 2-C-methyl-D-erythritol, 2-C-methyl-D-erythritol phosphate, in particular 2-C-methyl-D-erythritol 4-phosphate, 2-C-methyl-D-erythrose, 2-C-methyl-D-erythrose phosphate, in particular 2-C-methyl-D-erythrose 4-phosphate, and of phosphate and alcohol precursors, is detected.

14. Process according to claim 13, characterised in that phosphorylation of the following phosphates or alcohols is detected:



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15. Process for the combined determination of the enzymatic activity of DOXP synthase and of DOXP reductase, characterised in that the conversion of glyceraldehyde 3-phosphate into 2-C-methylerythritol 4-phosphate is detected.
16. Process for screening a compound for the treatment of infectious processes in humans and animals, wherein the process comprises:
- a) provision of a host cell which contains a recombinant expression vector, wherein the vector comprises at least a portion of the oligonucleotide sequence according to SEQ ID no. 1, SEQ ID no. 3 or SEQ ID no. 5 or variants or analogues thereof, and moreover of a compound suspected to have antimycotic, antibiotic, antiparasitic or antiviral action in humans and animals,
  - b) bringing the host cell into contact with the compound and
  - c) determining the antimicrobial, antimycotic, antibiotic, antiparasitic or antiviral action of the compound.
17. Process for screening for compounds for treating plants, wherein the process comprises:
- a) provision of a host cell which contains a recombinant expression vector, wherein the vector comprises at least a portion of the oligonucleotide sequence according to SEQ ID no. 1, SEQ ID no. 3 or SEQ ID no. 5 or variants or analogues thereof, and moreover of a compound suspected to have antimicrobial,

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antiviral, antiparasitic, bactericidal,  
fungicidal or herbicidal action in plants,

b) bringing the host cell into contact with the  
compound and

5 c) determining the antimicrobial, antiviral,  
antiparasitic, bactericidal, fungicidal or  
herbicidal action of the compound.

10 18. Use of DNA according to one of claims 1 to 5 or of  
proteins according to one of claims 9 to 12 or of  
transgenic systems according to claim 7 for the  
prevention or treatment of diseases in humans and  
animals.

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Genes of the 1-deoxy-D-xylulose biosynthesis pathway

The present invention relates to DNA sequences which, when incorporated into the genome of viruses, eukaryotes and prokaryotes, modify isoprenoid biosynthesis and to a genetic engineering process for the production of these transgenic viruses, eukaryotes and prokaryotes. The invention also relates to a process for the identification of substances having herbicidal, antimicrobial, antiparasitic, antiviral, fungicidal, bactericidal action in plants and antimicrobial, antiparasitic, antimycotic, antibacterial and antiviral action in humans and animals.

The biosynthesis pathway for the formation of isoprenoids via the classical acetate/mevalonate pathway and an alternative mevalonate-independent biosynthesis pathway, the deoxy-D-xylulose phosphate pathway is already known (Rohmer, M., Knani, M., Simonin, P., Sutter, B. and Sahm, H. (1993): *Biochem. J.* 295: 517-524).

It is, however, not known how and by which pathways it is possible to bring about a change in the isoprenoid concentration in viruses, eukaryotes and prokaryotes by means of the deoxy-D-xylulose phosphate pathway. Figure 1 shows this biosynthesis pathway.

DNA sequences are consequently provided which code for 1-deoxy-D-xylulase 5-phosphate synthase (DOXP synthase), 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DOXP reductoisomerase) or the gcpE protein. All three genes and enzymes are involved in isoprenoid biosynthesis.

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(Translator's comment: The portion at the beginning of the next paragraph enclosed in square brackets corresponds to the beginning of the sentence which finishes on page 2, line 1 of the original).

[The gcpE protein has a kinase function and catalyses the phosphorylation of a sugar or a phosphorus sugar or a precursor of isoprenoid biosynthesis, in particular the phosphorylation of 2-C-methyl-D-erythritol, 2-C-methyl-D-erythritol phosphate, in particular 2-C-methyl-D-erythritol 4-phosphate, 2-C-methyl-D-erythrose, 2-C-methyl-D-erythrose] phosphate, in particular 2-C-methyl-D-erythrose 4-phosphate. In the precursor of isoprenoid synthesis, the gcpE protein in particular catalyses the phosphorylation of the following substances:

$\text{CH}_2(\text{OH})-\text{C}(\text{CH}_3)=\text{C}(\text{OH})-\text{CH}_2-\text{O}-\text{PO}(\text{OH})_2,$   
 $\text{CH}_2(\text{OH})-\text{C}(\text{CH}_3)=\text{C}(\text{OH})-\text{CH}_2-\text{OH},$   
 $\text{CH}_2(\text{OH})-\text{CH}(\text{CH}_3)-\text{CO}-\text{CH}_2-\text{O}-\text{PO}(\text{OH})_2,$   
 $\text{CH}_2(\text{OH})-\text{CH}(\text{CH}_3)-\text{CO}-\text{CH}_2\text{OH}$   
 $\text{CH}_2=\text{C}(\text{CH}_3)-\text{CO}-\text{CH}_2-\text{O}-\text{PO}(\text{OH})_2,$   
 $\text{CH}_2=\text{C}(\text{CH}_3)-\text{CO}-\text{CH}_2-\text{OH},$   
 $\text{CH}_2=\text{C}(\text{CH}_3)-\text{CH}(\text{OH})-\text{CH}_2-\text{O}-\text{PO}(\text{OH})_2,$   
 $\text{CH}_2=\text{C}(\text{CH}_3)-\text{CH}(\text{OH})-\text{CH}_2-\text{OH},$   
 $\text{CH}_2(\text{OH})-\text{C}(=\text{CH}_2)-\text{C}(\text{OH})-\text{CH}_2-\text{O}-\text{PO}(\text{OH})_2,$   
 $\text{CH}_2(\text{OH})-\text{C}(=\text{CH}_2)-\text{C}(\text{OH})-\text{CH}_2-\text{OH}$   
 $\text{CHO}-\text{CH}(\text{CH}_3)-\text{CH}(\text{OH})-\text{CH}_2-\text{O}-\text{PO}(\text{OH})_2,$   
 $\text{CHO}-\text{CH}(\text{CH}_3)-\text{CH}(\text{OH})-\text{CH}_2-\text{OH},$   
 $\text{CH}_2(\text{OH})-\text{C}(\text{OH})(\text{CH}_3)-\text{CH}=\text{CH}-\text{O}-\text{PO}(\text{OH})_2,$   
 $\text{CH}_2(\text{OH})-\text{C}(\text{OH})(\text{CH}_3)-\text{CH}=\text{CH}-\text{OH}$   
 $\text{CH}(\text{OH})=\text{C}(\text{CH}_3)-\text{CH}(\text{OH})-\text{CH}_2-\text{O}-\text{PO}(\text{OH})_2,$   
 $\text{CH}(\text{OH})=\text{C}(\text{CH}_3)-\text{CH}(\text{OH})-\text{CH}_2-\text{OH},$   
 $(\text{CH}_3)_2\text{HC}-\text{CO}-\text{CH}_2-\text{O}-\text{PO}(\text{OH})_2,$   
 $(\text{CH}_3)_2\text{HC}-\text{CO}-\text{CH}_2-\text{O}-\text{H},$   
 $(\text{CH}_3)_2\text{HC}-\text{CH}(\text{OH})-\text{CH}_2-\text{O}-\text{PO}(\text{OH})_2,$   
 $(\text{CH}_3)_2\text{HC}-\text{CH}(\text{OH})-\text{CH}_2-\text{O}-\text{H}.$

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DOXP synthase catalyses the condensation of pyruvate and glyceraldehyde 3-phosphate to yield 1-deoxy-D-xylulose 5-phosphate and DOXP reductoisomerase catalyses the  
5 conversion of 1-deoxy-D-xylulose 5-phosphate into 2-C-methyl-D-erythritol 4-phosphate (c.f. Fig. 1).

The invention relates to the following DNA sequences:  
DNA sequences which code for a polypeptide with the amino  
10 acid sequence shown in SEQ ID no. 2 or for an analogue or derivative of the polypeptide according to SEQ ID no. 2, in which one or more amino acids have been deleted, added or replaced by other amino acids, wherein the enzymatic action of the polypeptide is retained, and which  
15 sequences originate from parasites, wherein sequence variations occurring within the framework of natural strain variability are included,

DNA sequences which code for a polypeptide with the amino  
20 acid sequence shown in SEQ ID no. 4 or for an analogue or derivative of the polypeptide according to SEQ ID no. 4, in which one or more amino acids have been deleted, added or replaced by other amino acids, wherein the enzymatic action of the polypeptide is retained, and which  
25 sequences originate from parasites, wherein sequence variations occurring within the framework of natural strain variability are included,

and DNA sequences which code for a polypeptide with the  
30 amino acid sequence shown in SEQ ID no. 6 or for an analogue or derivative of the polypeptide according to SEQ ID no. 6, in which one or more amino acids have been

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deleted, added or replaced by other amino acids, wherein the catalytic function of the polypeptide is retained.

25 . The genes and the gene products thereof (polypeptides) are shown with their primary structure and are assigned as follows:

SEQ ID no. 1: 1-deoxy-D-xylulose 5-phosphate reducto-  
isomerase gene

30 SEQ ID no. 2: 1-deoxy-D-xylulose 5-phosphate reducto-  
isomerase

SEQ ID no. 3: 1-deoxy-D-xylulose 5-phosphate synthase  
gene

SEQ ID no. 4: 1-deoxy-D-xylulose 5-phosphate synthase

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SEQ ID no. 5: gcpE gene

SEQ ID no. 6: gcpE proteins.

5 The DNA sequences all originate from *Plasmodium falciparum*.

10 Apart from the DNA sequences stated in the sequence listing, suitable sequences are also those which, as a result of the degeneration of the genetic code, have another DNA sequence, but code for the same peptide or for an analogue or derivative of the polypeptide, in which one or more amino acids have been deleted, added or replaced by other amino acids.

15 The sequences according to the invention are suitable for the expression of genes in viruses, eukaryotes and prokaryotes which are responsible for isoprenoid biosynthesis in the 1-deoxy-D-xylulose pathway.

20 According to the invention, eukaryotes or eukaryotic cells include animal cells, plant cells, algae, yeasts, fungi, while prokaryotes or prokaryotic cells include bacteria, archaeobacteria and eubacteria.

25 When a DNA sequence is incorporated into a genome on which the above-stated DNA sequence is located, expression of the above-described genes in viruses, eukaryotes and prokaryotes is enabled. The viruses, eukaryotes and prokaryotes transformed according to the invention are cultivated in a manner known per se and the  
30 isoprenoid formed during such cultivation is isolated and optionally purified. Not all isoprenoids need to be

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isolated as in some case the isoprenoids are released directly into the ambient air.

The invention furthermore relates to a process for the production of transgenic viruses, eukaryotes and prokaryotes in order to modify the isoprenoid content, which process comprises the following steps.

- a) Production of a DNA sequence with the following sub-sequences
  - i) promoter which is active in viruses, eukaryotes and prokaryotes and ensures the formation of an RNA in the intended target tissue or target cells,
  - ii) DNA sequence which codes for a polypeptide with the amino acid sequence shown in SEQ ID no. 2, 4 or 6 or for an analogue or derivative of the polypeptide according to SEQ ID no. 2, 4 or 6,
  - iii) 5' and 3' untranslated sequence which enables or enhances expression of the stated genes in viruses, eukaryotes and prokaryotes,
- b) transfer and incorporation of the DNA sequence into the genome of viruses, prokaryotic or eukaryotic cells with or without the use of a vector (for example plasmid, viral DNA).

The intact, whole plants may be regenerated from plant cells transformed in this manner.

- 30 The protein-coding sequences with the nucleotide sequences SEQ ID no. 1, SEQ ID no. 3 and SEQ ID no. 5 may be provided with a promoter which ensures transcription in certain organs or cells, which promoter is coupled in

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sense orientation (3' end of the promoter to the 5' end of the coding sequence) to the sequence which codes the protein to be formed. A termination signal which determines termination of mRNA synthesis is attached to the 3' end of the coding sequence. In order to direct the protein which is to be expressed to certain subcellular compartments, such as chloroplasts, amyloplasts, mitochondria, vacuoles, cytosol or intercellular spaces, a further sequence which codes for a so-called signal sequence or a transit peptide may be inserted between the promoter and the coding sequence. In some cases, it is necessary to insert sequences which code for a signal at the COOH terminus of the protein. The sequence must be in the same reading frame as the coding sequence of the protein. A large number of cloning vectors is available in order to prepare for the introduction of the DNA sequences according to the invention into higher plants, which vectors contain a replication signal for *E. coli* and a marker which permits selection of the transformed cells. Depending upon the method by which desired genes are introduced into the plant, further DNA sequences may be required. If, for example, the Ti or Ri plasmid is used to transform the plant cells, at least one right border, but frequently the right border and left border of the Ti and Ri plasmid T-DNA must be inserted as a flanking region into the genes to be introduced. The use of T-DNA for transforming plant cells has been intensively investigated and comprehensively described in EP 120516; Hoekama in "The Binary Plant Vector System", Offset-drukkerij Kanthers B.V. Alblasserdam (1985), chapter V; Fraley et al., *Crit.Rev.Plant Sci.* 4, 1-46 and An et al. (1985) *EMBO J.* 4, 277-287. Once the introduced DNA has been incorporated into the genome, it is

generally stable and is also retained in the descendants of the originally transformed cells. It normally contains a selection marker, which imparts to the transformed plant cells resistance to a biocide or an antibiotic, such as kanamycin, G 418, bleomycin, hygromycin or phosphinotricin and others. The particular marker used is thus intended to allow selection of transformed cells from cells lacking the inserted DNA.

Many techniques are available for introducing DNA into a plant. These techniques include transformation with the assistance of agrobacteria, for example *Agrobacterium tumefaciens*, protoplast fusion, microinjection of DNA, electroporation, as well as ballistic methods and virus infection. Whole plants may then be regenerated from the transformed plant material in a suitable medium which may contain antibiotics or biocides for selection purposes. No particular requirements are placed upon the plasmids for injection and electroporation. However, if whole plants are to be regenerated from such transformed cells, a selectable marker gene must be present. The transformed cells grow in the plants in the conventional manner (McCormick et al. (1986), *Plant Cell Reports* 5, 81-84). The plants may be cultivated normally and be crossed with plants which have the same transformed genome or other genomes. The resultant individuals have the corresponding phenotypic properties.

The present invention also provides expression vectors which contain one or more of the DNA sequences according to the invention. Such expression vectors are obtained by providing the DNA sequences according to the invention with suitable functional regulation signals. Such

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regulation signals are DNA sequences which are responsible for expression, for example promoters, operators, enhancers, ribosomal binding sites, and are recognised by the host organism.

5

Further regulation signals, which for example control replication or recombination of the recombinant DNA in the host organism, may optionally also be a constituent part of the expression vector.

10

The host organisms transformed with the DNA sequences or expression vectors according to the invention are also provided by the present invention.

15

Suitable host cells and organisms for expressing the enzymes according to the invention are those which comprise no intrinsic enzymes with the function of DOXP synthase, DOXP reductoisomerase or the gcpE protein. This is the case for archaebacteria, animals, fungi, slime moulds and some eubacteria. The absence of such intrinsic enzyme activity substantially facilitates detection and purification of the recombinant enzymes. As a consequence, it is also for the first time possible straightforwardly to measure, in crude extracts from the host cells, the activity and in particular the inhibition of the activity of the recombinant enzymes according to the invention by various chemicals and pharmaceuticals.

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The enzymes according to the invention are advantageously then expressed in eukaryotic cells if post-translational modification and native folding of the polypeptide chain is to be achieved. Moreover, depending upon the expression system, it is ensured when expressing genomic

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DNA sequences that introns are eliminated by splicing the DNA and the enzymes are produced in the polypeptide sequences characteristic to the parasites. Using recombinant DNA techniques, sequences coding for introns may be eliminated from or inserted for experimental purposes into the DNA sequences to be expressed.

The protein may be isolated from the host cell or the culture supernatant of the host cell using methods known to the person skilled in the art. *In vitro* reactivation of the enzymes may also be required.

In order to facilitate purification, the enzymes according to the invention or sub-sequences of the enzymes may be expressed as fusion proteins with various peptide chains. Oligo-histidine sequences and sequences derived from glutathione S-transferase, thioredoxin or calmodulin-binding peptides are particularly suitable for this purpose.

The enzymes according to the invention or sub-sequences of the enzymes may furthermore be expressed as fusion proteins with such peptide chains known to the person skilled in the art that the recombinant enzymes are transported into the extracellular medium or into certain compartments of the host cells. Both purification and investigation of the biological activity of the enzymes may consequently be facilitated.

When expressing the enzymes according to the invention, it may prove convenient to modify individual codons. Purposeful replacement of bases in the coding region may here also be advisable if the codons used in the

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parasites differ from the codon use in the heterologous expression system, in order to ensure optimal synthesis of the protein.

5 The enzymes according to the invention may furthermore be obtained under standardised conditions by *in vitro* translation by methods known to the person skilled in the art. Systems suitable for this purpose are rabbit reticulocyte and wheat germ extracts and bacterial  
10 lysates. *In vitro* transcribed mRNA may also be translated into *Xenopus* oocytes.

Oligo- and polypeptides, the sequences of which are derived from the peptide sequence of the enzymes  
15 according to the invention, may be obtained by chemical synthesis. Given appropriate selection of the sequences, such peptides have properties which are characteristic of the enzymes according to the invention. Such peptides may be produced in large quantities and are particularly  
20 suitable for investigating the kinetics of enzyme activity, regulation of enzyme activity, the three-dimensional structure of the enzymes, inhibition of enzyme activity by various chemicals and pharmaceuticals and the binding geometry and binding affinity of various  
25 ligands.

DNA with the nucleotides from sequences SEQ ID no. 1, 3 and 5 are preferably used for the recombinant production of the enzymes according to the invention.

30 The invention accordingly moreover relates to a process for screening for compounds which inhibit the deoxy-D-xylulose phosphate metabolic pathway. According to this

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process, a host organism, which contains a recombinant expression vector, wherein the vector comprises at least a portion of the oligonucleotide sequence according to SEQ ID no. 1, SEQ ID no. 3 or SEQ ID no. 5 or variants or homologues thereof, is provided, as is a compound which is suspected to have antimicrobial, antiparasitic, antibacterial, antiviral and antimycotic action in humans and animals or an antimicrobial, antiviral, bactericidal, herbicidal or fungicidal activity in plants. The host organism is then brought into contact with the compound and the activity of the compound determined.

The present invention also provides methods for determining the enzymatic activity of the gcpE protein. Said activity may be determined using known methods. Determination is performed by detecting the phosphorylation of a sugar or of a phosphorus sugar or of a precursor of isoprenoid biosynthesis, in particular the phosphorylation of 2-C-methyl-D-erythritol, 2-C-methyl-D-erythritol phosphate, in particular 2-C-methyl-D-erythritol 4-phosphate, 2-C-methyl-D-erythrose, 2-C-methyl-D-erythrose phosphate, in particular 2-C-methyl-D-erythrose 4-phosphate. The present invention also provides the use of this measurement method for identifying substances which inhibit the activity of the particular enzymes.

The enzymatic activity of DOXP synthase and DOXP reductoisomerase may be detected in a single step by determining the conversion of glyceraldehyde 3-phosphate into 2-C-methylerythritol 4-phosphate.

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Determination of the activities of DOXP synthase and DOXP reductoisomerase proceeds analogously. Fluorimetric methods described by Querol et al. are also suitable for determining DOXP synthase activity (Querol et al.,  
5 abstracts, 4<sup>th</sup> European Symposium on Plant Isoprenoids, Barcelona, 21-23 April 1999).

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## SEQUENCE LISTING

&lt;110&gt; Jomaa, Hassan

&lt;120&gt; Genes of the 1-deoxy-D-xylulose biosynthesis pathway

&lt;130&gt; 15696

&lt;140&gt; PCT/EP99

&lt;141&gt; 1999-09-22

&lt;150&gt; DE19923567.8

&lt;151&gt; 1999-05-22

&lt;150&gt; DE19843279.8

&lt;151&gt; 1998-09-22

&lt;160&gt; 6

&lt;170&gt; PatentIn Ver. 2.1

&lt;210&gt; 1

&lt;211&gt; 1467

&lt;212&gt; DNA

&lt;213&gt; Plasmodium falciparum

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(1467)

&lt;220&gt;

&lt;221&gt; gene

&lt;222&gt; (1)..(1467)

&lt;220&gt;

&lt;221&gt; mRNA

&lt;222&gt; (1)..(1467)

&lt;400&gt; 1

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1 5 10 15	

aat gat tta gta ata aat aat aca tca aaa tgt gtt tcc att gaa aga	96
Asn Asp Leu Val Ile Asn Asn Thr Ser Lys Cys Val Ser Ile Glu Arg	
20 25 30	

aga aaa aat aac gca tat ata aat tat ggt ata gga tat aat gga cca	144
Arg Lys Asn Asn Ala Tyr Ile Asn Tyr Gly Ile Gly Tyr Asn Gly Pro	
35 40 45	

gat aat aaa ata aca aag agt aga aga tgt aaa aga ata aag tta tgc	192
Asp Asn Lys Ile Thr Lys Ser Arg Arg Cys Lys Arg Ile Lys Leu Cys	
50 55 60	

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aaa aag gat tta ata gat att ggt gca ata aag aaa cca att aat gta	240
Lys Lys Asp Leu Ile Asp Ile Gly Ala Ile Lys Lys Pro Ile Asn Val	
65 70 75 80	
gca att ttt gga agt act ggt agt ata ggt acg aat gct tta aat ata	288
Ala Ile Phe Gly Ser Thr Gly Ser Ile Gly Thr Asn Ala Leu Asn Ile	
85 90 95	
ata agg gag tgt aat aaa att gaa aat gtt ttt aat gtt aaa gca ttg	336
Ile Arg Glu Cys Asn Lys Ile Glu Asn Val Phe Asn Val Lys Ala Leu	
100 105 110	
tat gtg aat aag agt gtg aat gaa tta tat gaa caa gct aga gaa ttt	384
Tyr Val Asn Lys Ser Val Asn Glu Leu Tyr Glu Gln Ala Arg Glu Phe	
115 120 125	
tta cca gaa tat ttg tgt ata cat gat aaa agt gta tat gaa gaa tta	432
Leu Pro Glu Tyr Leu Cys Ile His Asp Lys Ser Val Tyr Glu Glu Leu	
130 135 140	
aaa gaa ctg gta aaa aat ata aaa gat tat aaa cct ata ata ttg tgt	480
Lys Glu Leu Val Lys Asn Ile Lys Asp Tyr Lys Pro Ile Ile Leu Cys	
145 150 155 160	
ggg gat gaa ggg atg aaa gaa ata tgt agt agt aat agt ata gat aaa	528
Gly Asp Glu Gly Met Lys Glu Ile Cys Ser Ser Asn Ser Ile Asp Lys	
165 170 175	
ata gtt att ggt att gat tct ttt caa gga tta tat tct act atg tat	576
Ile Val Ile Gly Ile Asp Ser Phe Gln Gly Leu Tyr Ser Thr Met Tyr	
180 185 190	
gca att atg aat aat aaa ata gtt gcg tta gct aat aaa gaa tcc att	624
Ala Ile Met Asn Asn Lys Ile Val Ala Leu Ala Asn Lys Glu Ser Ile	
195 200 205	
gtc tct gct ggt ttc ttt tta aag aaa tta tta aat att cat aaa aat	672
Val Ser Ala Gly Phe Phe Leu Lys Lys Leu Leu Asn Ile His Lys Asn	
210 215 220	
gca aag ata ata cct gtt gat tca gaa cat agt gct ata ttt caa tgt	720
Ala Lys Ile Ile Pro Val Asp Ser Glu His Ser Ala Ile Phe Gln Cys	
225 230 235 240	
tta gat aat aat aag gta tta aaa aca aaa tgt tta caa gac aat ttt	768
Leu Asp Asn Asn Lys Val Leu Lys Thr Lys Cys Leu Gln Asp Asn Phe	
245 250 255	
tct aaa att aac aat ata aat aaa ata ttt tta tgt tca tct gga ggt	816
Ser Lys Ile Asn Asn Ile Asn Lys Ile Phe Leu Cys Ser Ser Gly Gly	
260 265 270	
cca ttt caa aat tta act atg gac gaa tta aaa aat gta aca tca gaa	864
Pro Phe Gln Asn Leu Thr Met Asp Glu Leu Lys Asn Val Thr Ser Glu	
275 280 285	

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- 3 -

aat gct tta aag cat cct aaa tgg aaa atg ggt aag aaa ata act ata 912  
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 290 295 300

gat tct gca act atg atg aat aaa ggt tta gag gtt ata gaa acc cat 960  
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 305 310 315 320

ttt tta ttt gat gta gat tat aat gat ata gaa gtt ata gta cat aaa 1008  
 Phe Leu Phe Asp Val Asp Tyr Asn Asp Ile Glu Val Ile Val His Lys  
 325 330 335

gaa tgc att ata cat tct tgt gtt gaa ttt ata gac aaa tca gta ata 1056  
 Glu Cys Ile Ile His Ser Cys Val Glu Phe Ile Asp Lys Ser Val Ile  
 340 345 350

agt caa atg tat tat cca gat atg caa ata ccc ata tta tat tct tta 1104  
 Ser Gln Met Tyr Tyr Pro Asp Met Gln Ile Pro Ile Leu Tyr Ser Leu  
 355 360 365

aca tgg cct gat aga ata aaa aca aat tta aaa cct tta gat ttg gct 1152  
 Thr Trp Pro Asp Arg Ile Lys Thr Asn Leu Lys Pro Leu Asp Leu Ala  
 370 375 380

cag gtt tca act ctt aca ttt cat aaa cct tct tta gaa cat ttc ccg 1200  
 Gln Val Ser Thr Leu Thr Phe His Lys Pro Ser Leu Glu His Phe Pro  
 385 390 395 400

tgt att aaa tta gct tat caa gca ggt ata aaa gga aac ttt tat cca 1248  
 Cys Ile Lys Leu Ala Tyr Gln Ala Gly Ile Lys Gly Asn Phe Tyr Pro  
 405 410 415

act gta cta aat gcg tca aat gaa ata gct aac aac tta ttt ttg aat 1296  
 Thr Val Leu Asn Ala Ser Asn Glu Ile Ala Asn Asn Leu Phe Leu Asn  
 420 425 430

aat aaa att aaa tat ttt gat att tcc tct ata ata tcg caa gtt ctt 1344  
 Asn Lys Ile Lys Tyr Phe Asp Ile Ser Ser Ile Ile Ser Gln Val Leu  
 435 440 445

gaa tct ttc aat tct caa aag gtt tcg gaa aat agt gaa gat tta atg 1392  
 Glu Ser Phe Asn Ser Gln Lys Val Ser Glu Asn Ser Glu Asp Leu Met  
 450 455 460

aag caa att cta caa ata cat tct tgg gcc aaa gat aaa gct acc gat 1440  
 Lys Gln Ile Leu Gln Ile His Ser Trp Ala Lys Asp Lys Ala Thr Asp  
 465 470 475 480

ata tac aac aaa cat aat tct tca tag 1467  
 Ile Tyr Asn Lys His Asn Ser Ser  
 485

&lt;210&gt; 2

&lt;211&gt; 488

&lt;212&gt; PRT

&lt;213&gt; Plasmodium falciparum

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- 4 -

&lt;400&gt; 2

Met Lys Lys Tyr Ile Tyr Ile Tyr Phe Phe Phe Ile Thr Ile Thr Ile  
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 20 25 30  
 Arg Lys Asn Asn Ala Tyr Ile Asn Tyr Gly Ile Gly Tyr Asn Gly Pro  
 35 40 45  
 Asp Asn Lys Ile Thr Lys Ser Arg Arg Cys Lys Arg Ile Lys Leu Cys  
 50 55 60  
 Lys Lys Asp Leu Ile Asp Ile Gly Ala Ile Lys Lys Pro Ile Asn Val  
 65 70 75 80  
 Ala Ile Phe Gly Ser Thr Gly Ser Ile Gly Thr Asn Ala Leu Asn Ile  
 85 90 95  
 Ile Arg Glu Cys Asn Lys Ile Glu Asn Val Phe Asn Val Lys Ala Leu  
 100 105 110  
 Tyr Val Asn Lys Ser Val Asn Glu Leu Tyr Glu Gln Ala Arg Glu Phe  
 115 120 125  
 Leu Pro Glu Tyr Leu Cys Ile His Asp Lys Ser Val Tyr Glu Glu Leu  
 130 135 140  
 Lys Glu Leu Val Lys Asn Ile Lys Asp Tyr Lys Pro Ile Ile Leu Cys  
 145 150 155 160  
 Gly Asp Glu Gly Met Lys Glu Ile Cys Ser Ser Asn Ser Ile Asp Lys  
 165 170 175  
 Ile Val Ile Gly Ile Asp Ser Phe Gln Gly Leu Tyr Ser Thr Met Tyr  
 180 185 190  
 Ala Ile Met Asn Asn Lys Ile Val Ala Leu Ala Asn Lys Glu Ser Ile  
 195 200 205  
 Val Ser Ala Gly Phe Phe Leu Lys Lys Leu Leu Asn Ile His Lys Asn  
 210 215 220  
 Ala Lys Ile Ile Pro Val Asp Ser Glu His Ser Ala Ile Phe Gln Cys  
 225 230 235 240  
 Leu Asp Asn Asn Lys Val Leu Lys Thr Lys Cys Leu Gln Asp Asn Phe  
 245 250 255  
 Ser Lys Ile Asn Asn Ile Asn Lys Ile Phe Leu Cys Ser Ser Gly Gly  
 260 265 270  
 Pro Phe Gln Asn Leu Thr Met Asp Glu Leu Lys Asn Val Thr Ser Glu  
 275 280 285  
 Asn Ala Leu Lys His Pro Lys Trp Lys Met Gly Lys Lys Ile Thr Ile  
 290 295 300

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- 5 -

Asp Ser Ala Thr Met Met Asn Lys Gly Leu Glu Val Ile Glu Thr His  
 305 310 315 320  
 Phe Leu Phe Asp Val Asp Tyr Asn Asp Ile Glu Val Ile Val His Lys  
 325 330 335  
 Glu Cys Ile Ile His Ser Cys Val Glu Phe Ile Asp Lys Ser Val Ile  
 340 345 350  
 Ser Gln Met Tyr Tyr Pro Asp Met Gln Ile Pro Ile Leu Tyr Ser Leu  
 355 360 365  
 Thr Trp Pro Asp Arg Ile Lys Thr Asn Leu Lys Pro Leu Asp Leu Ala  
 370 375 380  
 Gln Val Ser Thr Leu Thr Phe His Lys Pro Ser Leu Glu His Phe Pro  
 385 390 395 400  
 Cys Ile Lys Leu Ala Tyr Gln Ala Gly Ile Lys Gly Asn Phe Tyr Pro  
 405 410 415  
 Thr Val Leu Asn Ala Ser Asn Glu Ile Ala Asn Asn Leu Phe Leu Asn  
 420 425 430  
 Asn Lys Ile Lys Tyr Phe Asp Ile Ser Ser Ile Ile Ser Gln Val Leu  
 435 440 445  
 Glu Ser Phe Asn Ser Gln Lys Val Ser Glu Asn Ser Glu Asp Leu Met  
 450 455 460  
 Lys Gln Ile Leu Gln Ile His Ser Trp Ala Lys Asp Lys Ala Thr Asp  
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 Ile Tyr Asn Lys His Asn Ser Ser  
 485

&lt;210&gt; 3

&lt;211&gt; 3872

&lt;212&gt; DNA

&lt;213&gt; Plasmodium falciparum

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (126)..(3740)

&lt;220&gt;

&lt;221&gt; gene

&lt;222&gt; (1)..(3870)

&lt;220&gt;

&lt;221&gt; mRNA

&lt;222&gt; (1)..(3870)

&lt;400&gt; 3

ggtaatatat gtataatata tatataatat attcttacgt atgtatcatt tatgaatcat 60

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- 6 -

aataatattc taaatttacc ttccggtttt gctcgatctt ctcattttcg ttccagcttt 120  
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Met Ile Phe Asn Tyr Val Phe Phe Lys Asn Phe Val Pro Val Val  
1 5 10 15  
cta tac att ctc ctt ata ata tat att aac tta aat ggc atg aat aat 218  
Leu Tyr Ile Leu Leu Ile Ile Tyr Ile Asn Leu Asn Gly Met Asn Asn  
20 25 30  
aaa aat caa ata aaa aca gaa aaa att tat ata aag aaa ttg aat agg 266  
Lys Asn Gln Ile Lys Thr Glu Lys Ile Tyr Ile Lys Lys Leu Asn Arg  
35 40 45  
ttg tca agg aaa aat tcg tta tgt agt tct aaa aat aaa ata gca tgc 314  
Leu Ser Arg Lys Asn Ser Leu Cys Ser Ser Lys Asn Lys Ile Ala Cys  
50 55 60  
ttg ttc gat ata gga aat gat gat aat aga aat acg aca tat ggc tat 362  
Leu Phe Asp Ile Gly Asn Asp Asp Asn Arg Asn Thr Thr Tyr Gly Tyr  
65 70 75  
aat gtg aat gtt aaa aat gat gat att aat tcc tta cta aaa aat aat 410  
Asn Val Asn Val Lys Asn Asp Asp Ile Asn Ser Leu Leu Lys Asn Asn  
80 85 90 95  
tat agt aat aaa ttg tac atg gat aag agg aaa aat att aat aat gta 458  
Tyr Ser Asn Lys Leu Tyr Met Asp Lys Arg Lys Asn Ile Asn Asn Val  
100 105 110  
att agt act aat aaa ata tct ggg tcc att tca aat att tgt agt aga 506  
Ile Ser Thr Asn Lys Ile Ser Gly Ser Ile Ser Asn Ile Cys Ser Arg  
115 120 125  
aat caa aaa gaa aat gaa caa aaa aga aat aaa caa aga tgt tta act 554  
Asn Gln Lys Lys Glu Asn Glu Gln Lys Arg Asn Lys Gln Arg Cys Leu Thr  
130 135 140  
caa tgt cac act tat aat atg tca cat gaa cag gac aaa cta gct aat 602  
Gln Cys His Thr Tyr Asn Met Ser His Glu Gln Asp Lys Leu Ala Asn  
145 150 155  
gat aat aat agg aat aat aaa aag aat ttt aat tta tta ttt ata aat 650  
Asp Asn Asn Arg Asn Asn Lys Lys Asn Phe Asn Leu Leu Phe Ile Asn  
160 165 170 175  
tat ttt aat ttg aaa cga atg aaa aat tct ctt cta aat aaa gac aat 698  
Tyr Phe Asn Leu Lys Arg Met Lys Asn Ser Leu Leu Asn Lys Asp Asn  
180 185 190  
ttc ttt tac tgt aaa gaa aaa aaa ttg tca ttt ctg cat aag gcc tat 746  
Phe Phe Tyr Cys Lys Glu Lys Lys Leu Ser Phe Leu His Lys Ala Tyr  
195 200 205  
aaa aaa aaa aat tgc act ttt caa aat tat agt tta aaa aga aaa tct 794  
Lys Lys Lys Asn Cys Thr Phe Gln Asn Tyr Ser Leu Lys Arg Lys Ser  
210 215 220

aat cgt gat tca cat aaa ttg ttt tct gga gaa ttt gac gat tat aca 842  
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 225 230 235

aat aat aat gct tta tat gaa tcc gaa aaa aaa gaa tac att aca cta 890  
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 260 265 270

aat gat aat aat gat tat aat aat aat aat agt tgt aat aat tta gga 986  
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 275 280 285

gag aga tcc aat cat tat gat aat tat ggt gga gat aat aat aat cca 1034  
 Glu Arg Ser Asn His Tyr Asp Asn Tyr Gly Gly Asp Asn Asn Asn Pro  
 290 295 300

tgt aat aat aat aat gac aaa tat gat ata gga aaa tat ttc aaa cag 1082  
 Cys Asn Asn Asn Asn Asp Lys Tyr Asp Ile Gly Lys Tyr Phe Lys Gln  
 305 310 315

att aat acc ttt att aat att gat gaa tat aaa act ata tat ggt gat 1130  
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 320 325 330 335

gaa ata tat aaa gaa ata tat gaa cta tat gta gaa aga aat att cct 1178  
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 340 345 350

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 355 360 365

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 370 375 380

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 Lys Glu Glu Phe Ile Asn Asn Gly Val Tyr Ile Asn Asn Ile Asp Asn  
 385 390 395

aca tat tat aaa aaa gaa aat att tta ata atg aaa aag ata tta cat 1370  
 Thr Tyr Tyr Lys Lys Glu Asn Ile Leu Ile Met Lys Lys Ile Leu His  
 400 405 410 415

tat ttc cca tta tta aaa tta att aat aat cca tca gat tta aaa aag 1418  
 Tyr Phe Pro Leu Leu Lys Leu Ile Asn Asn Pro Ser Asp Leu Lys Lys  
 420 425 430

tta aaa aaa caa tat tta cct tta tta gca cat gaa tta aaa ata ttt 1466  
 Leu Lys Lys Gln Tyr Leu Pro Leu Leu Ala His Glu Leu Lys Ile Phe  
 435 440 445

tta ttt ttt att gta aat ata aca gga ggt cat ttt tcc tct gtt tta 1514  
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 450 455 460

agc tct tta gaa att caa tta tta tta ttg tat att ttt aat caa cca 1562  
 Ser Ser Leu Glu Ile Gln Leu Leu Leu Tyr Ile Phe Asn Gln Pro  
 465 470 475

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 Tyr Asp Asn Val Ile Tyr Asp Ile Gly His Gln Ala Tyr Val His Lys  
 480 485 490 495

ata ttg acc gga aga aaa cta tta ttt cta tca tta aga aat aaa aaa 1658  
 Ile Leu Thr Gly Arg Lys Leu Leu Phe Leu Ser Leu Arg Asn Lys Lys  
 500 505 510

ggt att agt gga ttc cta aat att ttt gaa agt att tat gat aaa ttt 1706  
 Gly Ile Ser Gly Phe Leu Asn Ile Phe Glu Ser Ile Tyr Asp Lys Phe  
 515 520 525

ggg gct ggt cac agt tcc act tca tta agt gct ata caa gga tat tat 1754  
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 530 535 540

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 545 550 555

ata gaa ata agt gat aac gca aat gtc acg aat aat gaa agg ata ttt 1850  
 Ile Glu Ile Ser Asp Asn Ala Asn Val Thr Asn Asn Glu Arg Ile Phe  
 560 565 570 575

caa aaa gga ata cac aat gat aat aat att aac aat aat att aat aat 1898  
 Gln Lys Gly Ile His Asn Asp Asn Asn Ile Asn Asn Asn Ile Asn Asn  
 580 585 590

aat aat tat atc aat cct tca gat gtg gta gga aga gaa aat acg aat 1946  
 Asn Asn Tyr Ile Asn Pro Ser Asp Val Val Gly Arg Glu Asn Thr Asn  
 595 600 605

gta cca aat gta cga aat gat aac cat aac gtg gat aaa gta cac att 1994  
 Val Pro Asn Val Arg Asn Asp Asn His Asn Val Asp Lys Val His Ile  
 610 615 620

gct att ata gga gat ggt ggt tta aca ggt gga atg gca tta gaa gcg 2042  
 Ala Ile Ile Gly Asp Gly Gly Leu Thr Gly Gly Met Ala Leu Glu Ala  
 625 630 635

tta aat tat att tca ttc ttg aat tct aaa att tta att att tat aat 2090  
 Leu Asn Tyr Ile Ser Phe Leu Asn Ser Lys Ile Leu Ile Ile Tyr Asn  
 640 645 650 655

gat aac gga caa gtt tct tta cca aca aat gcc gta agt ata tca ggt 2138  
 Asp Asn Gly Gln Val Ser Leu Pro Thr Asn Ala Val Ser Ile Ser Gly  
 660 665 670

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- 9 -

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aat ata gaa gca aat gct ggt gat aat aaa tta tcg aaa aat gca aaa Asn Ile Glu Ala Asn Ala Gly Asp Asn Lys Leu Ser Lys Asn Ala Lys 690 695 700	2234
gag aat aac att ttt gaa aat ttg aat tat gat tat att ggt gtt gtg Glu Asn Asn Ile Phe Glu Asn Leu Asn Tyr Asp Tyr Ile Gly Val Val 705 710 715	2282
aat ggt aat aat aca gaa gag ctc ttt aaa gta tta aat aat ata aaa Asn Gly Asn Asn Thr Glu Glu Leu Phe Lys Val Leu Asn Asn Ile Lys 720 725 730 735	2330
gaa aat aaa tta aaa aga gct act gtt ctt cat gta cgt aca aaa aaa Glu Asn Lys Leu Lys Arg Ala Thr Val Leu His Val Arg Thr Lys Lys 740 745 750	2378
tcg aat gat ttt ata aat tca aag agt cca ata agt ata ttg cac tct Ser Asn Asp Phe Ile Asn Ser Lys Ser Pro Ile Ser Ile Leu His Ser 755 760 765	2426
ata aag aaa aat gag att ttc cct ttc gat acc act ata tta aat gga Ile Lys Lys Asn Glu Ile Phe Pro Phe Asp Thr Thr Ile Leu Asn Gly 770 775 780	2474
aat att cat aag gag aac aag ata gaa gaa gag aaa aat gtg tct tca Asn Ile His Lys Glu Asn Lys Ile Glu Glu Glu Lys Asn Val Ser Ser 785 790 795	2522
tct aca aag tat gat gta aat aat aag aat aat aaa aat aat gat aat Ser Thr Lys Tyr Asp Val Asn Asn Lys Asn Asn Lys Asn Asn Asp Asn 800 805 810 815	2570
agt gaa att ata aaa tat gaa gat atg ttt tca aaa gag acg ttc aca Ser Glu Ile Ile Lys Tyr Glu Asp Met Phe Ser Lys Glu Thr Phe Thr 820 825 830	2618
gat ata tat aca aat gaa atg tta aaa tat tta aag aaa gat aga aat Asp Ile Tyr Thr Asn Glu Met Leu Lys Tyr Leu Lys Lys Asp Arg Asn 835 840 845	2666
ata ata ttc cta tct ccc gct atg tta gga gga tca gga ttg gtt aaa Ile Ile Phe Leu Ser Pro Ala Met Leu Gly Gly Ser Gly Leu Val Lys 850 855 860	2714
att agt gag cgt tat cca aat aat gta tat gat gta ggt ata gca gaa Ile Ser Glu Arg Tyr Pro Asn Asn Val Tyr Asp Val Gly Ile Ala Glu 865 870 875	2762
caa cat tct gta act ttc gca gca gct atg gca atg aat aag aaa tta Gln His Ser Val Thr Phe Ala Ala Ala Met Ala Met Asn Lys Lys Leu 880 885 890 895	2810

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 900 905 910

caa att ata cat gat ctt aat tta caa aat ata cct tta aag gtt ata 2906  
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 Ile Gly Arg Ser Gly Leu Val Gly Glu Asp Gly Ala Thr His Gln Gly  
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 Ile Tyr Asp Leu Ser Tyr Leu Gly Thr Leu Asn Asn Ala Tyr Ile Ile  
 945 950 955

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 Ser Pro Ser Asn Gln Val Asp Leu Lys Arg Ala Leu Arg Phe Ala Tyr  
 960 965 970 975

tta gat aag gac cat tct gtg tat ata cgt ata ccc aga atg aac ata 3098  
 Leu Asp Lys Asp His Ser Val Tyr Ile Arg Ile Pro Arg Met Asn Ile  
 980 985 990

tta agt gat aag tac atg aaa gga tat ttg aac att cat atg aaa aat 3146  
 Leu Ser Asp Lys Tyr Met Lys Gly Tyr Leu Asn Ile His Met Lys Asn  
 995 1000 1005

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aat gaa cat tat tca agc aga gga gat aca cag aca aaa aaa aaa aaa 3338  
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 1090 1095 1100

tca att gtt gat atg ata ttt tta aat cct tta gat aaa aat atg ata 3482  
 Ser Ile Val Asp Met Ile Phe Leu Asn Pro Leu Asp Lys Asn Met Ile  
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- 11 -

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Asp His Val Ile Lys Gln Asn Lys His Gln Tyr Leu Ile Thr Tyr Glu  
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gat aat act ata ggt ggt ttt tct aca cat ttc aat aat tat tta ata 3578  
Asp Asn Thr Ile Gly Gly Phe Ser Thr His Phe Asn Asn Tyr Leu Ile  
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Glu Asn Asn Tyr Ile Thr Lys His Asn Leu Tyr Val His Asn Ile Tyr  
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Leu Ser Asn Glu Pro Ile Glu His Ala Ser Phe Lys Asp Gln Gln Glu  
1170 1175 1180  
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Val Val Lys Met Asp Lys Cys Ser Leu Val Asn Arg Ile Lys Asn Tyr  
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Ser Arg Lys Asn Ser Leu Cys Ser Ser Lys Asn Lys Ile Ala Cys Leu  
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Phe Asp Ile Gly Asn Asp Asp Asn Arg Asn Thr Thr Tyr Gly Tyr Asn  
65 70 75 80  
Val Asn Val Lys Asn Asp Asp Ile Asn Ser Leu Leu Lys Asn Asn Tyr  
85 90 95  
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115 120 125

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Gln Lys Glu Asn Glu Gln Lys Arg Asn Lys Gln Arg Cys Leu Thr Gln  
 130 135 140  
 Cys His Thr Tyr Asn Met Ser His Glu Gln Asp Lys Leu Ala Asn Asp  
 145 150 155 160  
 Asn Asn Arg Asn Asn Lys Lys Asn Phe Asn Leu Leu Phe Ile Asn Tyr  
 165 170 175  
 Phe Asn Leu Lys Arg Met Lys Asn Ser Leu Leu Asn Lys Asp Asn Phe  
 180 185 190  
 Phe Tyr Cys Lys Glu Lys Lys Leu Ser Phe Leu His Lys Ala Tyr Lys  
 195 200 205  
 Lys Lys Asn Cys Thr Phe Gln Asn Tyr Ser Leu Lys Arg Lys Ser Asn  
 210 215 220  
 Arg Asp Ser His Lys Leu Phe Ser Gly Glu Phe Asp Asp Tyr Thr Asn  
 225 230 235 240  
 Asn Asn Ala Leu Tyr Glu Ser Glu Lys Lys Glu Tyr Ile Thr Leu Asn  
 245 250 255  
 Asn Asn Asn Lys Asn Asn Asn Asn Lys Asn Asn Asp Asn Lys Asn Asn  
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 Asp Asn Asn Asp Tyr Asn Asn Asn Asn Ser Cys Asn Asn Leu Gly Glu  
 275 280 285  
 Arg Ser Asn His Tyr Asp Asn Tyr Gly Gly Asp Asn Asn Asn Pro Cys  
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 Asn Thr Phe Ile Asn Ile Asp Glu Tyr Lys Thr Ile Tyr Gly Asp Glu  
 325 330 335  
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 340 345 350  
 Tyr Tyr Glu Arg Lys Tyr Phe Ser Glu Asp Ile Lys Lys Ser Val Leu  
 355 360 365  
 Phe Asp Ile Asp Lys Tyr Asn Asp Val Glu Phe Glu Lys Ala Ile Lys  
 370 375 380  
 Glu Glu Phe Ile Asn Asn Gly Val Tyr Ile Asn Asn Ile Asp Asn Thr  
 385 390 395 400  
 Tyr Tyr Lys Lys Glu Asn Ile Leu Ile Met Lys Lys Ile Leu His Tyr  
 405 410 415  
 Phe Pro Leu Leu Lys Leu Ile Asn Asn Pro Ser Asp Leu Lys Lys Leu  
 420 425 430

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Lys Lys Gln Tyr Leu Pro Leu Leu Ala His Glu Leu Lys Ile Phe Leu  
 435 440 445  
 Phe Phe Ile Val Asn Ile Thr Gly Gly His Phe Ser Ser Val Leu Ser  
 450 455 460  
 Ser Leu Glu Ile Gln Leu Leu Leu Leu Tyr Ile Phe Asn Gln Pro Tyr  
 465 470 475 480  
 Asp Asn Val Ile Tyr Asp Ile Gly His Gln Ala Tyr Val His Lys Ile  
 485 490 495  
 Leu Thr Gly Arg Lys Leu Leu Phe Leu Ser Leu Arg Asn Lys Lys Gly  
 500 505 510  
 Ile Ser Gly Phe Leu Asn Ile Phe Glu Ser Ile Tyr Asp Lys Phe Gly  
 515 520 525  
 Ala Gly His Ser Ser Thr Ser Leu Ser Ala Ile Gln Gly Tyr Tyr Glu  
 530 535 540  
 Ala Glu Trp Gln Val Lys Asn Lys Glu Lys Tyr Gly Asn Gly Asp Ile  
 545 550 555 560  
 Glu Ile Ser Asp Asn Ala Asn Val Thr Asn Asn Glu Arg Ile Phe Gln  
 565 570 575  
 Lys Gly Ile His Asn Asp Asn Asn Ile Asn Asn Asn Ile Asn Asn Asn  
 580 585 590  
 Asn Tyr Ile Asn Pro Ser Asp Val Val Gly Arg Glu Asn Thr Asn Val  
 595 600 605  
 Pro Asn Val Arg Asn Asp Asn His Asn Val Asp Lys Val His Ile Ala  
 610 615 620  
 Ile Ile Gly Asp Gly Gly Leu Thr Gly Gly Met Ala Leu Glu Ala Leu  
 625 630 635 640  
 Asn Tyr Ile Ser Phe Leu Asn Ser Lys Ile Leu Ile Ile Tyr Asn Asp  
 645 650 655  
 Asn Gly Gln Val Ser Leu Pro Thr Asn Ala Val Ser Ile Ser Gly Asn  
 660 665 670  
 Arg Pro Ile Gly Ser Ile Ser Asp His Leu His Tyr Phe Val Ser Asn  
 675 680 685  
 Ile Glu Ala Asn Ala Gly Asp Asn Lys Leu Ser Lys Asn Ala Lys Glu  
 690 695 700  
 Asn Asn Ile Phe Glu Asn Leu Asn Tyr Asp Tyr Ile Gly Val Val Asn  
 705 710 715 720  
 Gly Asn Asn Thr Glu Glu Leu Phe Lys Val Leu Asn Asn Ile Lys Glu  
 725 730 735

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Asn Lys Leu Lys Arg Ala Thr Val Leu His Val Arg Thr Lys Lys Ser  
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Asn Asp Phe Ile Asn Ser Lys Ser Pro Ile Ser Ile Leu His Ser Ile  
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Lys Lys Asn Glu Ile Phe Pro Phe Asp Thr Thr Ile Leu Asn Gly Asn  
 770 775 780

Ile His Lys Glu Asn Lys Ile Glu Glu Glu Lys Asn Val Ser Ser Ser  
 785 790 795 800

Thr Lys Tyr Asp Val Asn Asn Lys Asn Asn Lys Asn Asn Asp Asn Ser  
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Glu Ile Ile Lys Tyr Glu Asp Met Phe Ser Lys Glu Thr Phe Thr Asp  
 820 825 830

Ile Tyr Thr Asn Glu Met Leu Lys Tyr Leu Lys Lys Asp Arg Asn Ile  
 835 840 845

Ile Phe Leu Ser Pro Ala Met Leu Gly Gly Ser Gly Leu Val Lys Ile  
 850 855 860

Ser Glu Arg Tyr Pro Asn Asn Val Tyr Asp Val Gly Ile Ala Glu Gln  
 865 870 875 880

His Ser Val Thr Phe Ala Ala Ala Met Ala Met Asn Lys Lys Leu Lys  
 885 890 895

Ile Gln Leu Cys Ile Tyr Ser Thr Phe Leu Gln Arg Ala Tyr Asp Gln  
 900 905 910

Ile Ile His Asp Leu Asn Leu Gln Asn Ile Pro Leu Lys Val Ile Ile  
 915 920 925

Gly Arg Ser Gly Leu Val Gly Glu Asp Gly Ala Thr His Gln Gly Ile  
 930 935 940

Tyr Asp Leu Ser Tyr Leu Gly Thr Leu Asn Asn Ala Tyr Ile Ile Ser  
 945 950 955 960

Pro Ser Asn Gln Val Asp Leu Lys Arg Ala Leu Arg Phe Ala Tyr Leu  
 965 970 975

Asp Lys Asp His Ser Val Tyr Ile Arg Ile Pro Arg Met Asn Ile Leu  
 980 985 990

Ser Asp Lys Tyr Met Lys Gly Tyr Leu Asn Ile His Met Lys Asn Glu  
 995 1000 1005

Ser Lys Asn Ile Asp Val Asn Val Asp Ile Asn Asp Asp Val Asp Lys  
 1010 1015 1020

Tyr Ser Glu Glu Tyr Met Asp Asp Asp Asn Phe Ile Lys Ser Phe Ile  
 1025 1030 1035 1040

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Gly Lys Ser Arg Ile Ile Lys Met Asp Asn Glu Asn Asn Asn Thr Asn  
                     1045                    1050                    1055  
 Glu His Tyr Ser Ser Arg Gly Asp Thr Gln Thr Lys Lys Lys Lys Val  
                     1060                    1065                    1070  
 Cys Ile Phe Asn Met Gly Ser Met Leu Phe Asn Val Ile Asn Ala Ile  
                     1075                    1080                    1085  
 Lys Glu Ile Glu Lys Glu Gln Tyr Ile Ser His Asn Tyr Ser Phe Ser  
                     1090                    1095                    1100  
 Ile Val Asp Met Ile Phe Leu Asn Pro Leu Asp Lys Asn Met Ile Asp  
                     1105                    1110                    1115                    1120  
 His Val Ile Lys Gln Asn Lys His Gln Tyr Leu Ile Thr Tyr Glu Asp  
                     1125                    1130                    1135  
 Asn Thr Ile Gly Gly Phe Ser Thr His Phe Asn Asn Tyr Leu Ile Glu  
                     1140                    1145                    1150  
 Asn Asn Tyr Ile Thr Lys His Asn Leu Tyr Val His Asn Ile Tyr Leu  
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 Ser Asn Glu Pro Ile Glu His Ala Ser Phe Lys Asp Gln Gln Glu Val  
                     1170                    1175                    1180  
 Val Lys Met Asp Lys Cys Ser Leu Val Asn Arg Ile Lys Asn Tyr Leu  
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 Leu Leu Phe Tyr Ser His Val Lys Ile Lys Lys Leu Phe Ile Lys Ile  
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tct aat gta aac ata ttt ttt gca gaa gca aag aaa aat gga aaa aag	327
Ser Asn Val Asn Ile Phe Phe Ala Glu Ala Lys Lys Asn Gly Lys Lys	
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gaa ttc ttt ctt ttt tta cta aat ata aaa aaa aat agc caa cag aaa	375
Glu Phe Phe Leu Phe Leu Leu Asn Ile Lys Lys Asn Ser Gln Gln Lys	
45 50 55	
aaa act tat cat att acc aaa agg aat acc ata aat aaa agt gat ttt	423
Lys Thr Tyr His Ile Thr Lys Arg Asn Thr Ile Asn Lys Ser Asp Phe	
60 65 70 75	
tta tat tct tta cta aat gaa gaa ggg aat tct tca aaa aag gaa tat	471
Leu Tyr Ser Leu Leu Asn Glu Glu Gly Asn Ser Ser Lys Lys Glu Tyr	
80 85 90	
aaa aat tta aaa gat gaa gaa aaa tat aat atc ata caa aat ata aaa	519
Lys Asn Leu Lys Asp Glu Glu Lys Tyr Asn Ile Ile Gln Asn Ile Lys	
95 100 105	
aaa tat tgt gaa tgt act aaa aaa tat aaa agg ctc cca aca cga gaa	567
Lys Tyr Cys Glu Cys Thr Lys Lys Tyr Lys Arg Leu Pro Thr Arg Glu	
110 115 120	
gta gtt att gga aat gtt aaa att gga gga aat aat aaa ata gct att	615
Val Val Ile Gly Asn Val Lys Ile Gly Gly Asn Asn Lys Ile Ala Ile	
125 130 135	
caa act atg gct agc tgt gat aca aga aat gta gaa gaa tgt gta tat	663
Gln Thr Met Ala Ser Cys Asp Thr Arg Asn Val Glu Glu Cys Val Tyr	
140 145 150 155	
caa att aga aaa tgt aaa gat ttg ggt gct gac att gta agg ttg act	711
Gln Ile Arg Lys Cys Lys Asp Leu Gly Ala Asp Ile Val Arg Leu Thr	
160 165 170	
gtt caa gga gtt caa gaa gca caa gct agt tat cat att aaa gaa aaa	759
Val Gln Gly Val Gln Glu Ala Gln Ala Ser Tyr His Ile Lys Glu Lys	
175 180 185	
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Leu Leu Ser Glu Asn Val Asn Ile Pro Leu Val Ala Asp Ile His Phe	
190 195 200	
aat cct aaa ata gct tta atg gca gct gat gtg ttt gaa aaa att cga	855
Asn Pro Lys Ile Ala Leu Met Ala Ala Asp Val Phe Glu Lys Ile Arg	
205 210 215	
gtg aat cca gga aat tat gtt gat gga aga aaa aaa tgg ata gat aaa	903
Val Asn Pro Gly Asn Tyr Val Asp Gly Arg Lys Lys Trp Ile Asp Lys	
220 225 230 235	
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Val Tyr Lys Thr Lys Glu Glu Phe Asp Glu Gly Lys Leu Phe Ile Lys	
240 245 250	

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gaa aaa ttt gta cca tta att gaa aaa tgt aaa aga tta aat aga gca Glu Lys Phe Val Pro Leu Ile Glu Lys Cys Lys Arg Leu Asn Arg Ala 255 260 265	999
ata aga att gga aca aat cat gga tcc ctt tca tct cga gta tta tca Ile Arg Ile Gly Thr Asn His Gly Ser Leu Ser Ser Arg Val Leu Ser 270 275 280	1047
tat tat gga gat aca cca tta ggt atg gta gaa tcg gct ttt gag ttt Tyr Tyr Gly Asp Thr Pro Leu Gly Met Val Glu Ser Ala Phe Glu Phe 285 290 295	1095
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acc ata aaa gag tta gaa gat tct ctg caa att ttt aaa gat tta aat Thr Ile Lys Glu Leu Glu Asp Ser Leu Gln Ile Phe Lys Asp Leu Asn 460 465 470 475	1623

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495 500 505	
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510 515 520	
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525 530 535	
gat aat aat aat aat aat aat aat aat aat aat ata tta ttt tat gtg gat Asp Asn Asn Asn Asn Asn Asn Asn Asn Asn Ile Leu Phe Tyr Val Asp	1863
540 545 550 555	
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560 565 570	
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575 580 585	
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605 610 615	
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620 625 630 635	
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640 645 650	
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655 660 665	
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685 690 695	

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cat aga ctt ttg agc aga gtt gca tta aat tca ttt tta aca tta aat 2343  
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 720 725 730

tgc cca tct tgt gga aga act tta ttt aat ata caa gaa act act aaa 2439  
 Cys Pro Ser Cys Gly Arg Thr Leu Phe Asn Ile Gln Glu Thr Thr Lys  
 735 740 745

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 765 770 775

ggt tat gtt ggt agt gca cct aaa aaa att gat tta tat tat ggt aaa 2583  
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 780 785 790 795

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 800 805 810

ata gaa tta att aaa aaa cat aac aaa tgg aaa gat cca taaattgaat 2680  
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 815 820

atggacaagt atttatttat ttatttatct tatatataat atattataaa tttttcgatg 2740

tatttttcct tttaaaattt tttttttttt ttattttttt ttttgaagta atatttataa 2800

tgcatacata atattaaaat gtgtattata taataatattc attttattgt tattttaaaa 2860

gactaatacc aagaacaatt ttttaataat cattcttata acttggttaa tatatatata 2920

tatatatata tatttatitta tttatattta ttttatttta tttttggtat atgaaaagta 2980

aaaatataat aatttaaaag tatttacaaa ataaataata ttatatatct gtttttatat 3040

atatgttaat ggaaaaggag aaaataaata aataaaacaa acaaaataac atatatatat 3100

atatatatat actgaatgag aaagaaaaaa aaaagaaaag gatacga 3147

&lt;210&gt; 6

&lt;211&gt; 824

&lt;212&gt; PRT

&lt;213&gt; Plasmodium falciparum

&lt;400&gt; 6

Met Ser Tyr Ile Lys Arg Leu Ile Leu Phe Met Leu Leu Phe Tyr Ser  
 1 5 10 15

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His Val Lys Ile Lys Lys Leu Phe Ile Lys Ile Ser Asn Val Asn Ile  
 20 25 30  
 Phe Phe Ala Glu Ala Lys Lys Asn Gly Lys Lys Glu Phe Phe Leu Phe  
 35 40 45  
 Leu Leu Asn Ile Lys Lys Asn Ser Gln Gln Lys Lys Thr Tyr His Ile  
 50 55 60  
 Thr Lys Arg Asn Thr Ile Asn Lys Ser Asp Phe Leu Tyr Ser Leu Leu  
 65 70 75 80  
 Asn Glu Glu Gly Asn Ser Ser Lys Lys Glu Tyr Lys Asn Leu Lys Asp  
 85 90 95  
 Glu Glu Lys Tyr Asn Ile Ile Gln Asn Ile Lys Lys Tyr Cys Glu Cys  
 100 105 110  
 Thr Lys Lys Tyr Lys Arg Leu Pro Thr Arg Glu Val Val Ile Gly Asn  
 115 120 125  
 Val Lys Ile Gly Gly Asn Asn Lys Ile Ala Ile Gln Thr Met Ala Ser  
 130 135 140  
 Cys Asp Thr Arg Asn Val Glu Glu Cys Val Tyr Gln Ile Arg Lys Cys  
 145 150 155 160  
 Lys Asp Leu Gly Ala Asp Ile Val Arg Leu Thr Val Gln Gly Val Gln  
 165 170 175  
 Glu Ala Gln Ala Ser Tyr His Ile Lys Glu Lys Leu Leu Ser Glu Asn  
 180 185 190  
 Val Asn Ile Pro Leu Val Ala Asp Ile His Phe Asn Pro Lys Ile Ala  
 195 200 205  
 Leu Met Ala Ala Asp Val Phe Glu Lys Ile Arg Val Asn Pro Gly Asn  
 210 215 220  
 Tyr Val Asp Gly Arg Lys Lys Trp Ile Asp Lys Val Tyr Lys Thr Lys  
 225 230 235 240  
 Glu Glu Phe Asp Glu Gly Lys Leu Phe Ile Lys Glu Lys Phe Val Pro  
 245 250 255  
 Leu Ile Glu Lys Cys Lys Arg Leu Asn Arg Ala Ile Arg Ile Gly Thr  
 260 265 270  
 Asn His Gly Ser Leu Ser Ser Arg Val Leu Ser Tyr Tyr Gly Asp Thr  
 275 280 285  
 Pro Leu Gly Met Val Glu Ser Ala Phe Glu Phe Ser Asp Leu Cys Ile  
 290 295 300  
 Glu Asn Asn Phe Tyr Asn Leu Val Phe Ser Met Lys Ala Ser Asn Ala  
 305 310 315 320  
 Tyr Val Met Ile Gln Ser Tyr Arg Leu Leu Val Ser Lys Gln Tyr Glu

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325	330	335
Arg Asn Met Met Phe Pro Ile His Leu Gly Val Thr Glu Ala Gly Phe		
340	345	350
Gly Asp Asn Gly Arg Ile Lys Ser Tyr Leu Gly Ile Gly Ser Leu Leu		
355	360	365
Tyr Asp Gly Ile Gly Asp Thr Ile Arg Ile Ser Leu Thr Glu Asp Pro		
370	375	380
Trp Glu Glu Leu Thr Pro Cys Lys Lys Leu Val Glu Asn Leu Lys Lys		
385	390	395
Arg Ile Phe Tyr Asn Glu Asn Phe Lys Glu Asp Asn Glu Leu Lys Asn		
405	410	415
Asn Glu Met Asp Thr Lys Asn Leu Leu Asn Phe Glu Glu Asn Tyr Arg		
420	425	430
Asn Phe Asn Asn Ile Lys Lys Arg Asn Val Glu Lys Asn Asn Asn Val		
435	440	445
Leu His Glu Glu Cys Thr Ile Gly Asn Val Val Thr Ile Lys Glu Leu		
450	455	460
Glu Asp Ser Leu Gln Ile Phe Lys Asp Leu Asn Leu Glu Val Asp Ser		
465	470	475
Asn Gly Asn Leu Lys Lys Gly Ala Lys Thr Thr Asp Met Val Ile Ile		
485	490	495
Asn Asp Phe His Asn Ile Thr Asn Leu Gly Lys Lys Thr Val Asp Lys		
500	505	510
Leu Met Gln Val Gly Ile Asn Ile Val Val Gln Tyr Glu Pro His Asn		
515	520	525
Ile Glu Phe Ile Glu Lys Met Glu Pro Asn Asn Asp Asn Asn Asn Asn		
530	535	540
Asn Asn Asn Asn Asn Ile Leu Phe Tyr Val Asp Ile Lys Asn Ile Met		
545	550	555
Asn Ser Ser Glu Lys Asn Ile Lys Leu Ser Asn Ser Lys Gly Tyr Gly		
565	570	575
Leu Ile Leu Asn Gly Lys Glu Asp Ile Gln Thr Ile Lys Lys Ile Lys		
580	585	590
Glu Leu Asn Arg Arg Pro Leu Phe Ile Leu Leu Lys Ser Asp Asn Ile		
595	600	605
Tyr Glu His Val Leu Ile Thr Arg Arg Ile Asn Glu Leu Leu Gln Ser		
610	615	620
Leu Asn Ile Asn Ile Pro Tyr Ile His Tyr Val Asp Ile Asn Ser Asn		
625	630	635
		640

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Asn Tyr Asp Asp Ile Leu Val Asn Ser Thr Leu Tyr Ala Gly Ser Cys  
 645 650 655  
 Leu Met Asp Leu Met Gly Asp Gly Leu Ile Val Asn Val Thr Asn Asp  
 660 665 670  
 Val Leu Thr Asn Lys Lys Lys Ile Glu Thr Lys Tyr Asp Glu Lys Glu  
 675 680 685  
 Glu Val Glu Glu Glu Gly Asn Asn Lys Asp Ile His Arg Leu Leu Ser  
 690 695 700  
 Arg Val Ala Leu Asn Ser Phe Leu Thr Leu Asn Ile Leu Gln Asp Thr  
 705 710 715 720  
 Arg Ile Arg Leu Phe Lys Thr Asp Tyr Ile Ala Cys Pro Ser Cys Gly  
 725 730 735  
 Arg Thr Leu Phe Asn Ile Gln Glu Thr Thr Lys Lys Ile Met Lys Leu  
 740 745 750  
 Thr Gly His Leu Lys Gly Val Lys Ile Ala Val Met Gly Cys Ile Val  
 755 760 765  
 Asn Gly Ile Gly Glu Met Ala Asp Ala His Phe Gly Tyr Val Gly Ser  
 770 775 780  
 Ala Pro Lys Lys Ile Asp Leu Tyr Tyr Gly Lys Glu Leu Val Glu Arg  
 785 790 795 800  
 Asn Ile Pro Glu Glu Glu Ala Cys Asp Lys Leu Ile Glu Leu Ile Lys  
 805 810 815  
 Lys His Asn Lys Trp Lys Asp Pro  
 820